REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-66 are pending in the application. Claims 29-31, 37-45 and 59-66 are withdrawn from consideration as being drawn to non-elected inventions. Claims 46-51 and 55-56 are allowable except for the compounds of formula I. Claims 1-7, 13-28, 32, 33, 52-54, and 57-58 are rejected. Claims 8-12 and 34-36 are objected to as depending from rejected claims. Claims 8, 10, 19, 34, 46, 52, 55 and 57 have been amended to delete reference to the non-elected inventions eg. the compounds of Group I, and to better clarify what Applicants regard as the invention. New claims 67-72 have been added to incorporate the subject matter of original claims 2-7, which were originally dependent from rejected claim 1, now canceled. The new claims are now dependent from claim 8. No new matter has been added by way of this amendment. Thus, as a result of the foregoing amendment, claims 8-12, 19-28, 34-36, 46-58, and 67-72 remain under consideration.

Claims 8, 10, and 34 were amended in response to the Examiner's suggestion that these claims would be allowable if rewritten in independent form including all of the limitations of the rejected base claim and by canceling the non-elected inventions. Claims 19, 52 and 57 were amended in response to the Examiner's rejection under 35 U.S.C. §112, written description requirement. Support for these amendments can be found in the specification on page 38, lines 13-19, page 45, lines 27-28 and on page 46, lines 8-12. Claims 46 and 55 were amended to cancel the compound of Formula I, drawn to non-elected subject matter.

Support for new claim 67 is found in original claim 2.

Support for new claim 68 is found in original claim 3.

Support for new claim 69 is found in original claim 4.

Support for new claim 70 is found in original claim 5.

Support for new claim 71 is found in original claim 6.

Support for new claim 72 is found in original claim 7.

Claim Rejections under 35 U.S.C. §112

Claims 1-7, 13-28, 32-33, 52-54 and 57-58 are rejected under 35 U.S.C. §112, first paragraph for lack of written description. Applicants respectfully traverse the rejection and have canceled claims 1-7, 13-18, and 32-33.

Furthermore, Applicants have amended claim 19 to read on "...recovery of behavioral function of neurons...", support for which can be found in the specification on page 38, lines 13-19. Claim 52 has been amended to read on "...inducing neuronal replacement for treating...", the support for which can be found on page 38, lines 13-16. Claim 57 has been amended to read on "...neural precursor cells...", support for which can be found in the specification on page 45, lines 27-28 continuing on to page 46, lines 8-12.

The Examiner alleges that while the specification provides sufficient disclosure with respect to the activity of the claimed compounds represented by formula II for promoting neural regeneration or neural expression and the administration of bone marrow cells that have been treated with said compounds to the site of injury for the treatment of spinal cord injury by promoting neural regeneration or neural expression, the specification does not provide adequate representation regarding the claimed compounds in promoting regeneration of liver, pancreatic or muscle cells. In addition, the Examiner alleges that the specification does not provide sufficient written description to support the genus encompassed by these claims. While Applicants respectfully traverse the Examiner's rejection, claims 1-7, and 13-18 have been canceled without prejudice or disclaimer in order to place the application in condition for allowance.

Furthermore, the Examiner alleges that the instant specification fails to provide written description for the instantly claimed method for promoting increased neuronal function after a decrease in neuronal function due to trauma, injury or a neurodegenerative disease or condition. In addition, the Examiner alleges that the specification fails to provide sufficient written description for the skilled artisan to determine that the regeneration of neural tissue would provide the claimed method of promoting increased neuronal function or for treating a neurodegenerative condition or disease.

Applicants have amended the claims to better clarify what they believe to be the invention and provide herewith for the Examiner's convenience abstracts citing the use of neural stem cells and/or neural progenitor cells, that is, the cells induced by the compounds of the present invention, as neuroreplacement therapy in relevant animal models of neurodegenerative diseases. The complete articles, which were published after the filing of the present invention, have been ordered and will be forwarded to the Examiner upon receipt.

As noted in several of the abstracts provided, the transplantation of neural precursor cells into injured or diseased animals resulted in recovery of neuronal function, with the type of functional recovery defined by the model in which the cells were tested. For example, Applicants draw the Examiner's attention to the abstracts in Appendix A, attached herewith; in particular, Chiba et al, wherein the authors note that motoneuron-enriched neural progenitor cells obtained by culturing mouse embryonic stem cells with retinoic acid were transplanted into hemiplegic mice, which resulted in improvement of motor function in these mice. Furthermore, the abstract by Parati et al. demonstrates that intrastriatal engraftment of neural stem cells gives rise to dopaminergic-like neurons which results in long lasting functional recovery in the 6HODA model for Parkinson's disease. In addition, the abstract by Riess et al. demonstrates that transplanted neural stem cells survive, differentiate and improve neurological motor function in a mouse model of traumatic brain injury. And finally, the abstract by Zhao et al. demonstrates that human bone marrow stem cells exhibit neural phenotypes and are capable of ameliorating neurological deficits after grafting into the ischemic brain of rats. In particular, these stem cells having neural phenotypes were able to restore sensorimotor function after experimental stroke.

It is apparent from the literature presented that neural stem/precursor cells are capable of restoring neuronal function in various models of neurodegenerative diseases and conditions, including traumatic brain injury, spinal cord injury, stroke and Parkinson's disease. Accordingly, the compounds of the present invention promote neural stem/precursor cell proliferation as shown by the expression of neural stem/precursor cell markers, such as eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4. Therefore, it would stand to reason that due to the profound effect of the compounds of the present

invention on induction of neural stem cell/precursor cell proliferation, these compounds would be effective in restoration of neuronal function upon either direct administration of the compound to the mammal having experienced a traumatic brain or spinal cord injury or other neurodegenerative disease which results in neuronal dysfunction, or administration of bone marrow cells (as a source of stem cells) obtained from animals having been administered one of the compounds of the present invention. One of skill in the art would be aware of the potential neuronal functional recovery that may be attributed to administration of such compounds, whether it be recovery of motor function or cognitive function. Due to the pluripotent nature of the neuronal stem/precursor cells induced by the compounds of the present invention, restoration of multiple neuronal functions would be expected and these functions would vary depending upon the particular animal model used.

Claim 57 has been amended to read on "A method for promoting regeneration of neural precursor cells...", which is supported in the specification in Example 3, on page 45, lines 27-28 and on page 46, lines 8-12, wherein it is demonstrated that spinal cord injured animals treated with bone marrow cells (which are a source of stem cells) from animals treated with the test compound of formula II show cells immunoreactive with anti-nestin antibody at the site of the contusion, nestin being a cell surface marker for neural precursor cells. Thus, the test compound has served to promote regeneration of neural precursor cells (as shown by nestin positivity) from the stem cell population.

Accordingly, based on the claim amendments, arguments and references presented, withdrawal of the rejection under 35 U.S.C. §112 is respectfully requested.

Rejections Under 35 USC § 102(b)

The Examiner has rejected claims 1-7 under 35 USC § 102(b) as being anticipated by Nair et al. (U.S. Patent No. 4,965,284). Applicants respectfully traverse the Examiner's rejection, and have canceled claims 1-7 without prejudice or disclaimer, thereby rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

Allowable Subject Matter

Claim Objections

The Examiner has objected to claims 8-12 and 34-36 as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and if canceling non-elected inventions.

Applicants have made the claim amendments and have canceled non-elected inventions as suggested by the Examiner and have added new claims 67-72, which originally depended from claim 1, now canceled. The new claims are now dependent from claim 8, as amended. No new matter has been introduced by way of these amendments.

Allowable Claims

The Examiner has noted that claims 46-51 and 55-56 are allowable except for the compounds of Formula I, which have been withdrawn from further consideration as being drawn to a non-elected invention. Applicant has amended these claims to delete the compound of formula I as suggested by the Examiner.

Fees

A check in the amount of $55 for a one-month extension of time is enclosed as a small entity. No other fees are believed to be required, but if so, the Commissioner is hereby authorized to charge any fees, or credit any overpayment, to Deposit Account No. 11-1153.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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Enclosures: Appendix A, containing 4 abstracts by Chiba et al, Parati et al, Riess et al, and Zhao et al.

APPENDIX A

1: Cell Transplant. 2003;12(5):457-68.

Related Articles, Links

Transplantation of motoneuron-enriched neural cells derived from mouse embryonic stem cells improves motor function of hemiplegic mice.

Chiba S, Iwasaki Y, Sekino H, Suzuki N.

Department of Immunology, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan.

Embryonic stem (ES) cells are expected to be a potential donor source for neural transplantation. We have obtained motoneuron-enriched neural progenitor cells by culturing mouse ES cells with retinoic acid (RA). The cells also expressed mRNA of a neurotrophic factor, neurotrophin-3 (NT-3). The left motor cortex area of mice was damaged by cryogenic brain injury, and the neural cells were transplanted underneath the injured motor cortex, neighboring to the paraventricular region. We found that the cells expressing neuronal phenotypes not only remained close to the implantation site, but also exhibited substantial migration penetrating into the damaged lesion, in a seemingly directed manner up to cortical region. We found that some of the neural cells differentiated into Islet1-positive motoneurons. It seems likely that the ability of the ES cell-derived neural progenitor cells to respond in vivo to guidance cues and signals that can direct their migration and differentiation may contribute to functional recovery of the recipient mice. We found that an "island of the mature neuronal cells" of recipient origin emerged in the damaged motor cortex. This may be associated with the neuroprotective effects of the ES cell-derived neural cells. The ES cells differentiated into CD31+ vasculoendothelial cells with the RA treatment in vitro. Furthermore, the grafted cells may provide sufficient neurotrophic factors such as NT-3 for neuroprotection and regeneration. The grafted neural cells that migrated into residual cortex and differentiated into neurons had purposefully elongated axons that were stained with anti-neurofilament middle chain (NFM) antibody. Our study suggests that motoneurons can be induced from ES cells, and ES cells become virtually an unlimited source of cells for experimental and clinical neural cell transplantation.

PMID: 12953919 [PubMed - indexed for MEDLINE]

1: J Neurosurg Sci. 2003 Mar;47(1):8-17.

Neural stem cells. Biological features and therapeutic potential in Parkinson's disease.

Parati EA, Bez A, Ponti D, Sala S, Pozzi S, Pagano SF.

Laboratory of Neurobiology, National Neurological Institute C. Besta, Milan, Italy. parati@istituto.besta.it

AIM: Neural stem cells (NSC) are clonogenic cells, capable of self-renewal and multilineage differentiation, since, under the appropriated experimental conditions, they proliferate indefinitely as undifferentiated neurospheres or differentiate in neurons, astrocytes and oligodendrocytes. Parkinson's disease is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. METHODS: Here we investigated the suitability of recently identified and characterized neuronal progenitor cells at eliciting functional recovery in unilateral 6HODA-lesioned mice. We describe herein that intrastriatal engraftment of stem cell-derived neurons isolated from the olfactory bulb to give rise dopaminergic-like neurons results in long lasting functional recovery in 6OHDA-injured mice. RESULTS: Unilateral injection of 6OHDA resulted in a progressive neurodegeneration of the nigro-striatal pathway. Likewise, the systemic administration of L-DOPA in these mice elicited a marked contralateral turning which was evident 1 week post, increased during the following week and than stabilize throughout the time of the experiment. Conversely, the intrastriatal implantation of partially differentiated stem cells at 14 days postlesion, resulted in a profound decrease in L-DOPA-induced circling behavior; interestingly, the effect was evident 1 week after the engraftment and was retained during the following 9 weeks. Detailed biochemical and immunohistochemical evaluation is currently under investigation in our laboratory. Conclusion. Our observation opens new perspectives for the treatment of neurodegeneration in Parkinson's disease.

PMID: 12900727 [PubMed - indexed for MEDLINE]

1: Neurosurgery. 2002 Oct;51(4):1043-52; discussion 1052-4.

Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury.

Riess P, Zhang C, Saatman KE, Laurer HL, Longhi LG, Raghupathi R, Lenzlinger PM, Lifshitz J, Boockvar J, Neugebauer E, Snyder EY, McIntosh TK.

The Head Injury Center, Department of Neurosurgery, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.

OBJECTIVE: Using the neural stem cell (NSC) clone C17.2, we evaluated the ability of transplanted murine NSCs to attenuate cognitive and neurological motor deficits after traumatic brain injury. METHODS: Nonimmunosuppressed C57BL/6 mice (n = 65) were anesthetized and subjected to lateral controlled cortical impact brain injury (n = 52) or surgery without injury (sham operation group, n = 13). At 3 days postinjury, all brain-injured animals were reanesthetized and randomized to receive stereotactic injection of NSCs or control cells (human embryonic kidney cells) into the cortex-hippocampus interface in either the ipsilateral or the contralateral hemisphere. One group of animals (n = 7) was killed at either 1 or 3 weeks postinjury to assess NSC survival in the acute posttraumatic period. Motor function was evaluated at weekly intervals for 12 weeks in the remaining animals, and cognitive (i.e., learning) deficits were assessed at 3 and 12 weeks after transplantation. RESULTS: Brain-injured animals that received either ipsilateral or contralateral NSC transplants showed significantly improved motor function in selected tests as compared with human embryonic kidney cell-transplanted animals during the 12-week observation period. Cognitive dysfunction was unaffected by transplantation at either 3 or 12 weeks postinjury. Histological analyses showed that NSCs survive for as long as 13 weeks after transplantation and were detected in the hippocampus and/or cortical areas adjacent to the injury cavity. At 13 weeks, the NSCs transplanted ipsilateral to the impact site expressed neuronal (NeuN) or astrocytic (glial fibrillary acidic protein) markers but not markers of oligodendrocytes (2'3'cyclic nucleotide 3'-phosphodiesterase), whereas the contralaterally transplanted NSCs expressed neuronal but not glial markers (double-labeled immunofluorescence and confocal microscopy). CONCLUSION: These data suggest that transplanted NSCs can survive in the traumatically injured brain, differentiate into neurons and/or glia, and attenuate motor dysfunction after traumatic brain injury.

PMID: 12234415 [PubMed - indexed for MEDLINE]

1: Exp Neurol. 2002 Mar;174(1):11-20.

Related Articles, Links

ELSEVIER

Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats.

Zhao LR, Duan WM, Reyes M, Keene CD, Verfaillie CM, Low WC.

Department of Neurosurgery, University of Minnesota, 55455, USA.

There is now evidence to suggest that bone marrow mesenchymal stem cells (MSCs) not only differentiate into mesodermal cells, but can also adopt the fate of endodermal and ectodermal cell types. In this study, we addressed the hypotheses that human MSCs can differentiate into neural cells when implanted in the brain and restore sensorimotor function after experimental stroke. Purified human MSCs were grafted into the cortex surrounding the area of infarction 1 week after cortical brain ischemia in rats. Two and 6 weeks after transplantation animals were assessed for sensorimotor function and then sacrificed for histological examination. Ischemic rats that received human MSCs exhibited significantly improved functional performance in limb placement test. Histological analyses revealed that transplanted human MSCs expressed markers for astrocytes (GFAP(+)), oligodendroglia (GalC (+)), and neurons (beta III(+), NF160(+), NF200(+), hNSE(+), and hNF70(+)). The morphological features of the grafted cells, however, were spherical in nature with few processes. Therefore, it is unlikely that the functional recovery observed by the ischemic rats with human MSC grafts was mediated by the integration of new "neuronal" cells into the circuitry of the host brain. The observed functional improvement might have been mediated by proteins secreted by transplanted hMSCs, which could have upregulated host brain plasticity in response to experimental stroke.

PMID: 11869029 [PubMed - indexed for MEDLINE]